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Group B Streptococci in Human Disease[1]

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INTRODUCTION

History and Nomenclature

Bovine pathogens of economic and epidemiological importance (110) were recognized in the genus *Streptococcus* long before the definitive characterization studies of Lancefield (86). Seroclassification on the basis of cell wall carbohydrate antigens placed *Streptococcus agalactiae* (96), the species responsible for bovine mastitis, into streptococcal group B. Despite the subsequent review by Rantz (119) calling attention to the association of non-group A streptococci with human disease, clinical attention was focused primarily on group A and group D streptococcal pathogens for almost three decades, whereas group B organisms were only rarely considered as agents of human infections (60, 67, 93). The group B streptococci were recognized as commensals among the normal flora of the human upper respiratory tract and of the female genitourinary tract. In view of this role, Brown suggested designation of the human group B organisms as *S. opportunus* (27). The designation *S. mastitidis* has also appeared in the literature in association with bovine strains (65, 107). However, the widely accepted species nomenclature for all group B streptococci remains *S. agalactiae* (28).

Human Disease

Within the last decade, there has been an increasing awareness of the role of these organisms in the etiology of neonatal infection and in a spectrum of human pathological conditions (21, 29, 43, 55, 56, 68, 73, 76, 77, 84, 109, 116,

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131, 155). The recent emergence of group B streptococci as significant agents in neonatal sepsis accompanies a relative decline in isolation of coliform organisms (153). Historically, several shifts have occurred in the principal organisms causing neonatal disease: the classical group A beta-hemolytic streptococci had been reduced in incidence by the use of antibiotics to which the organisms were exquisitely sensitive; *Staphylococcus aureus* strains gradually exhibited remarkable virulence for neonates and resistance to multiple antibiotic agents; and, subsequently, coliforms replaced *S. aureus* in frequency during the 1960s. The report of a recent 12-institution Neonatal Meningitis Cooperative Study confirms the latest shift: the etiological agent in 38% of 131 cases of neonatal meningitis surveyed was *Escherichia coli*, but group B streptococci caused 31% of the cases (76).

The reason for the emergence of group B streptococci as etiological agents of neonatal disease remains unclear. Failures in isolation and misidentification of the group B organisms by the clinical laboratory and physician errors in interpretation of the significance of non-group A isolates must be acknowledged (18, 123, 149). Colonization rates in the female genitourinary tract have remained fairly constant (7, 19, 23, 29, 58, 67, 73, 82, 93, 109, 123, 133). Changes in hospital nursery techniques, as for example, relaxation of visitor restrictions and decreased use of hexachlorophene bathing, elude definitive implication, as does alteration of the relative vaginal flora by oral contraceptive usage (105, 153). Several group B serotypes are associated with neonatal disease, and thus single-strain mutation to virulence seems unlikely. The organism still exhibits marked susceptibility to penicillin, and usage of penicillin during pregnancy remains unchanged.

This review will attempt to draw together the recent clinical, microbiological, and epidemiological aspects of the group B streptococci, in view of the renewed interest in them as human pathogens.

THE AGENT

Strains of Bovine and Human Origin

S. agalactiae is principally a microbe of bovine and human origin, although strains have been isolated from fish, dogs, piglets, and occasionally from other animal species (29, 152). There is no definitive evidence that infected cattle serve as a reservoir for transfer of the group B streptococci to humans. Indeed, studies can be cited demonstrating biochemical, biological, and serological differences between bovine and human strains. In a survey of 100 strains in Australia, Simmons and Keogh showed that human strains were more virulent for mice and unable to ferment lactose, whereas the less virulent bovine strains usually were fermenters (132). In a similar extensive study, El Ghoroury was able to separate bovine from human strains using metabolic and serological markers (45). Haug's examination of 265 Norwegian strains showed varying biochemical reaction patterns and distribution of serotypes (69). Butter and deMoor were able to isolate human, but not bovine, strains from the throats of dairy farm workers in the Netherlands, and they were able to produce mastitis in cows using a human strain (29). Pattison and colleagues in Britain were able to classify all of their human strains, but only 75% of their bovine strains could be typed by the precipitin method of Lancefield (114). In a serological study of 827 strains submitted to the World Health Organization International Reference Centre for Streptococcus Typing, Prague, Jelinkova and co-workers found a reversed frequency of bovine, in contrast to human, serotypes (77).

Seroclassification

Lancefield's work has provided a comprehensive classification of the streptococci (86–89, 91, 94, 95). Serogrouping is based on cell wall carbohydrate composition. The heat- and acid-stable group B components (formerly "C substance") possess a net negative charge and include galactose, hexosamine, and L-rhamnose residues, in an α-1,2 linkage, as the terminal antigenic moiety (28, 30, 34, 51, 130). Typing within the B group is based upon envelope carbohydrate (formerly "S substance") from acid-heat extracts, rather than protein antigens as for group A. Reactivity is assessed by immunoprecipitation and mouse protection studies. The typing scheme for group B organisms originally described by Lancefield in 1934 designated three antigenic clusters of human and bovine isolates: I, II, and III (87). This was followed by recognition of distinct antigenic moieties within type I and a subdivision of this type into Ia and Ib (89). In a similar classification of bovine strains, Stableforth described 16 types differentiated by several immunoassays (135, 136). Pattison and colleagues utilized Lancefield's classification scheme and introduced two protein moieties, R and X, to reduce the numbers of strains untypable with the Lancefield reagents (113). Since they observed a complexity of serological cross-reactivity with Ia and Ib, Wilkinson and Moody proposed that an inter-

mediate type (Ii) be included in the typing battery (151). The Ii designation (now Ic) does not represent unique antigenic specificity, but rather antigens shared with other strains in the type I complex, as shown in Table 1. Chemical composition of the hydrochloric acid-extracted carbohydrate type antigens is illustrated in Table 2. Recently, Baker and Kasper demonstrated the acid lability and sialic acid composition of the type III antigen subjected to a milder extraction process (13, 15). The R and X protein antigens are unstable and cross-reactive. R antigen from group B type III is found also in streptococci of group A type 28 (95, 146). The Ibc protein, composed of two antigenic moieties, is stable and present only in group B types Ib, Ic, II, and rarely in III (147, 148).

Virulence Factors

In contrast to M proteins of other streptococcal groups, the R and X protein antigens appear unrelated to virulence, and specific antibodies to them show no passive protection capacities in animal challenge studies (147, 148). However, Lancefield and colleagues have recently demonstrated that antibodies to the Ibc protein antigen can be protective (94). It has been conclusively established that the carbohydrate type antigens are directly related to virulence, and specific anticarbohydrate antibodies provide passive protection in mice to challenge with homologous streptococci (87, 88, 92).

Two-thirds of group B strains studied by Tzannetis and associates produced bacteriocins (141). Recently, Tagg and colleagues purified and partially characterized a bacteriocin from group B streptococci (139). A soluble hemolysin, distinct from streptolysins S and O, is produced by hemolytic strains of *S. agalactiae* (28, 33). The extracellular enzyme hyaluronidase has been demonstrated in most strains (62). However, the function of these factors in pathogenesis is obscure.

As shown in Table 3, serotypes Ia and III are often associated with neonatal disease, and they seem to localize in the respiratory tract and central nervous system, respectively (8, 149). The classical virulence seen with the

TABLE 1. *Antigenic composition of group B streptococci*[a]

Antigenic determinants	Type				
	Ia	Ib	Ic(Ii)	II	III
Carbohydrate antigen	Ia	Ib	Ia	II	III
Protein antigen	None	Ibc[b]	Ibc	Ibc[c]	Ibc[d] R
Minor antigen	Common Iabc cross-reacting antigen[e]				

[a] From Wilkinson (146, 147), Wilkinson and Eagon (148), and Lancefield (87, 89, 94).
[b] May be composed of two distinct antigenic entities.
[c] Occasional (less than 1% of strains belong to the Ic/II complex) (148).
[d] Rare.
[e] Probable polysaccharide component of each of the main carbohydrate antigens within type I and common to all.

TABLE 2. *Carbohydrate composition of purified type antigens*[a]

Component	Antigen (% dry weight) of type:			
	Ia[b]	Ib[b]	II[c]	III[d]
Galactose	71.0	60.0	34.0	38.9
Glucosamine[e]	25.4	24.0	14.7	22.8
Glucose	0	0	27.2	17.8
Uronic acid	0	0	Not done	3.1
Sialic acid	0	0	Present, but not quantitated	24.0[f]
Immunodominant group[g]	*N*-acetylglucosamine	Glucosamine (unacetylated)	β-D-Galactopyranoside	Glucuronic acid

[a] Hydrochloric acid extracts.
[b] From Wilkinson (147).
[c] From Freimer (59).
[d] From Russell and Norcross (130).
[e] *N*-acetylated in Ia, Ib, II.
[f] From Baker and Kasper (13), neutral buffer washing, not hydrochloric acid, extraction method.
[g] Based on quantitative precipitin inhibition.

TABLE 3. *Prevalence of serological types in human group B streptococcal disease*

Source of isolate (age of patients)	Serotype (%)						Selected reference
	Ia	Ib	Ic	II	III	U[a]	
Neonate	45	14	NT[b]	21	19	0	Eickhoff et al. (43)[c]
	77	4	NT	0	19	0	Butter and deMoor (29)
<5 Days	3	4	12	36	43	3	Baker and Barrett (8)
>10 Days	0	0	5	0	95	0	Baker and Barrett (8)
Older child; adult	46	14	NT	7	23	9	Eickhoff et al. (43)[c]
	70	13	NT	4	4	9	Butter and deMoor (29)
	13	5	2	49	31	0	Baker and Barrett (7)[c]
	10	3	17	14	35	0[d]	Hafeez and Patterson[c, e]
Age not specified	11	20	NT	5	23	16	Jelinkova et al. (77)[c]
	20	8	7	19	32	22	Wilkinson et al. (149)[c]

[a] Not typable.
[b] NT, Not tested.
[c] Isolates not correlated with pathology.
[d] II/Ic cross-reactivity in 21% of strains in this study, indicating local prevalence and an increasing U. S. frequency of the II/Ic complex (H. Wilkinson, personal communication).
[e] Unpublished data.

group A streptococci is not found among the group B organisms; rather, they are opportunists whose pathogenicity is usually linked to some factor(s) of lowered host resistance: prematurity, hydrocephalus, diabetes, carcinoma, debilitation. It has been suggested that type III, found to be almost the exclusive cause of streptococcal neonatal meningitis, may have invasive properties linked to predilection for the central nervous system (8, 58) associated with capsular sialic acid (13, 14) as already demonstrated for certain *E. coli* strains (126). As shown in Table 4, the group B streptococci are typical commensals in man, present in varied niches of normal bacterial flora.

Metabolism

Carbohydrate metabolism among the group B organisms, as with all the streptococci, is chiefly homofermentative. Glucose is degraded to lactic acid via a hexose diphosphate pathway (28). In addition, Mickelson has described an oxidative pathway utilized by *S. agalactiae* (106). This aerobic metabolism of glucose, inhibited by cyanide and enhanced by aeration of cell suspensions, yields lactic acid, acetic acid, acetylmethylcarbinol, and carbon dioxide end products, and rarely trace amounts of pyruvic acid. No pentose phosphate or tricarboxylic acid cycle was found. Evidence from this investigation suggests that a noncytochrome iron-containing chromophore may participate in the electron transport system with oxygen as the terminal acceptor. Ritchey and Seeley have recently demonstrated a flavin-like, noncytochrome reduced nicotinamide adenine dinucleotide oxidase in the group B streptococci (125).

TABLE 4. *Rate of carriage in adults of group B streptococci*

Carrier rate[a]			Selected reference
Genital	Throat	Stool	
2.3	5	NT[b]	Lancefield and Hare (93), Hare (67)
NT	NT	5.5	Smith and Sherman (133)
5.2	NT	NT	Hood et al. (73)
12.4	NT	NT	Kexel and Beck (82)
NT	19.3	13.2	Butter and deMoor (29)
14.4	NT	NT	Bergqvist et al. (19)
29.8	5.8	NT	Baker and Barrett (7)
13.0	5.2	16.8	Franciosi et al. (58)
4.3	NT	NT	Niesen et al. (109)
18.0	NT	NT	Bevanger (23)
19.0[c]	NT	NT	Christensen et al. (32)
25.9	10.8	29.1	Hafeez and Patterson[d]
4.9	NT	NT	Reid (123)

[a] Percentage of specimens tested.
[b] NT, Not tested.
[c] Comprised of 22.3% of females and 11.7% of males tested.
[d] Unpublished data.

CLINICAL DISEASE SPECTRUM

Early Recognition

The attention that streptococci of groups A and D have received from bacteriologists and

physicians alike, although deserved, has obscured an appreciation for the medical significance of other streptococcal groups. However, immediately following reports of the definitive work on seroclassification of the streptococci, Lancefield and Hare (93) reviewed the clinical significance of non-group A isolates. These authors linked most severe maternal infections during the childbirth period with group A streptococci, but noted that of 18 milder infections after delivery, 7 were caused by group B streptococci. In 1938, Fry reported 9 cases of group B infection at a maternity hospital in London (60). The infections were fatal in three of the patients. Shortly thereafter in Australia, Hill and Butler (71) reviewed infections occurring after childbirth, and again the non-group A streptococci were implicated. In an examination of extrarespiratory streptococcal infections, Rantz (119) found that 75% were caused by streptococcal groups other than A. Subsequently, the involvement of the less well-known streptococci in infections at various sites in the human body was documented (57, 120, 121, 143).

In the early 1960s, sporadic reports again appeared in the literature of diverse types of infections attributed to non-group A or D streptococci (73, 100, 101, 124). The impact of group B streptococci was brought sharply into focus by the extensive study by Eickhoff and colleagues (43) at Boston City Hospital, where an increase in frequency of isolation of these organisms from neonates was uncovered. The organism was found to be the etiological agent in 25% of neonatal sepsis cases. In 1966, Feingold and associates at Massachusetts General Hospital surveyed 173 extrarespiratory streptococcal infections (51). The clinical and bacteriological data obtained from this study are summarized in Table 5, and show a significant etiological association of non-A or non-D streptococci in 40 to 48% of these infections. In examining 4,968 beta-hemolytic streptococcal isolates, without judgment as to clinical significance, Pollock and Dahlgren (115) noted the major contribution by group B strains: 8.6% of the upper respiratory, 29.3% of the lower respiratory, 71.2% of the genitourinary, and 4.3% of the wound isolates.

TABLE 5. *Serogroup and clinical significance of streptococcal isolates*[a]

Source	Clinically significant isolates		
	% of total	Groups A and D[b]	Other groups
Blood	78	52	B, C, G, H, K, NG[c]
Urine	72	60	B, C, NG
Wound	93	58	B, C, F, G, H, L, NG

[a] From Feingold et al. (51).
[b] Percentage of clinically significant isolates that were of groups A or D.
[c] Not groupable.

Neonatal Disease

Recent reemphasis on the association of group B streptococci with disease in neonates was provided by the brief case study of two infants with meningitis done by Kvittingen in Norway (84). Included in the report are observations that have subsequently been of prime importance in the development of our knowledge of these infections: that examination of the mothers of such infected newborns would be fruitful and that spread of infection can occur from an index case within the hospital nursery.

Franciosi and colleagues in Denver (58) and Baker and co-workers in Houston (8, 9), in reviewing large series of neonatal group B streptococcal infections, were able to separate infant disease into two clinical syndromes based on age at onset. Early-onset ("acute") infants presented with sepsis and respiratory distress within 5 days of birth, often within the first day of life. Late-onset ("delayed") infants presented with meningitis, with or without accompanying sepsis, usually after 10 days of age. In published cases in which adequate information is available, the clinical signs and symptoms of early- and late-onset disease merge into one another (9, 16, 20, 31, 58, 70, 75, 80, 84, 98, 100, 118, 140). Prematurity, as judged by gestational age or low birth weight (less than 2,500 g), appears to be a predisposing factor of late-onset disease (7, 8, 58, 118). The contributory effects of race and sex will be discussed in the later section on epidemiology. The influence of maternal complications of pregnancy on subsequent risk of neonatal group B disease remains equivocal, with reports ranging as high as 80% risk of disease after complications (43).

Mortality rates differ widely, as illustrated in Table 6, and reflect the type of clinical syndrome. Early-onset disease is more severely life threatening than late-onset type. The sequelae of neonatal group B disease, based upon available follow-up data, are tabulated in Table 7.

Unusual manifestations of group B streptococcal disease in the infant and young child include: asymptomatic bacteremia, impetigo,

TABLE 6. *Outcome of neonatal group B streptococcal disease*[a]

Mortality rate (%)	Selected reference
33	Hill and Butler (71)
62	Hood et al. (73)
40	Eickhoff et al. (43)
75	Butter and deMoor (29)
29	MacKnight et al. (99)
100	Rogers (128)
31	Bergqvist et al. (21)
58 Early 14 Late	Baker et al. (9)
18	Barton et al. (16)
71 Acute 45 Delayed	Franciosi et al. (58)
87	Hey et al. (70)
57 Early 18 Late	Baker and Barrett (8)
50 Early 33 Late	Horn et al. (74)
94	Quirante et al. (118)
50 Early 0 Late	Tseng and Kandall (140)
62	Ablow et al. (1)

[a] Unless otherwise indicated, represents overall group B streptococcal neonatal disease, including both sepsis and meningitis.

TABLE 7. *Outcome of neonatal group B streptococcal disease*[a]

Survivors with sequelae (%)[b]	Selected reference
9.1	Bergqvist et al. (21)
4.4	Baker et al. (9)
11.1-22.2	Barton et al. (16)
22.2	Horn et al. (75)
7.1	Bergquist (18)

[a] Overall group B streptococcal neonatal disease, both sepsis and meningitis.

[b] Sequelae in survivors included: retarded speech and language development, transient hemiparesis, retarded psychomotor development, febrile seizure disorder, hydrocephalus, and recurrent streptococcal infections.

otitis media, septic arthritis, osteomyelitis, ethmoiditis, cellulitis, and conjunctivitis (17, 46, 76).

Disease in Older Children and Adults

Although frequency and severity of infections due to group B streptococci decrease after infancy, the organism has been reported to be the etiological agent in a variety of clinical syndromes in the older patient. The spectrum of documented group B diseases after infancy includes: postpartum infection, urinary tract infection, bacteremia, gangrene, potentiation of autograft rejection, pneumonia, empyema, meningitis, endocarditis, peritonitis, osteomyelitis, arthritis, exudative pharyngitis, and omphalitis (2, 24, 29, 43, 54, 64, 97, 121, 134).

PATHOGENESIS

Perinatal Colonization

In both the human adult and infant, group B streptococci can be isolated from a variety of sites, often without associated pathology (26, 77, 109). Group B pathogenesis in the adult is usually linked to postpartum or urinary tract infections, or with diabetes, carcinoma, and other chronic or debilitating diseases (36, 43, 73, 120, 121, 149).

Association of neonatal colonization by group B organisms with subsequent invasion resulting in sepsis or meningeal disease has been a subject of controversy. The risk of a baby acquiring the organism from its genitally colonized mother and of a colonized baby demonstrating signs of streptococcal disease has not been clearly defined. Although several authors consider children born to carrier mothers to be at high risk (58, 73, 100), examination of available incidence data, as expressed in Table 8, indicates that the majority of colonized babies will not develop clinical illness. Risk factors affecting this outcome might include number of invading organisms, type and virulence of the organism, neonatal immune status, and other maternal or neonatal factors.

Early colonization of the neonate occurs intrapartum: either in utero from an ascending infection of the vagina or during delivery by passage through an infected birth canal (7, 8, 9, 58). Prolonged rupture of the fetal membranes during a difficult labor allows exposure of the fetus to organisms present in the amniotic fluid. Fetal hypoxia and gasping lead to aspiration or swallowing of infected amniotic fluid.

TABLE 8. *Incidence of group B streptococci/1,000 live births*

Neonatal colonization	Sepsis	Mortality	Selected reference
ND[a]	1.3	0.7	Eickhoff et al. (43)
90	ND	ND	Butter and deMoor (29)
262	2.9	ND	Baker and Barrett (7)
12	2	1	Franciosi et al. (58)
19	2.7	1	Reid (123)
650	3	ND	Yow (154)

[a] ND, Not done.

Breaking the integrity of the fetal skin by manipulation during delivery provides an additional vehicle for vertical transmission of organisms present in the fluid or birth canal. A recently documented additional mode of entry for organisms is via fetal monitoring scalp electrodes used during labor (111). These varied routes of early acquisition result in isolation of organisms from multiple sites in the infant, including the large and small intestines and stool, the lungs, and the skin. In early-onset disease, almost complete correlation has been observed when serotype identification of maternal and corresponding neonatal isolates of group B streptococci has been studied (8, 29, 58). Whether organisms enter via the intestinal or respiratory tracts or across the integumentary barrier, it is known that bacteremia results, and the neonate exhibits the cardinal sign of early-onset group B streptococcal disease, the picture of acute sepsis.

Histological evidence of the process of pathogenesis in early-onset disease shows prominent pulmonary pathology: interstitial hemorrhage, parenchymal exudate, interlobular lymphatics and alveoli containing polymorphonuclear neutrophils and gram-positive cocci, and in some instances hyaline membrane formation (1, 58, 70, 80, 142, 155).

Postnatal Colonization

Late or extrauterine acquisition of group B streptococci is now thought to be largely nosocomial in nature: intranursery spread from other neonates, from personnel, or from the mother (58, 84, 99, 137). As shown in Table 9, it has been documented that type III group B streptococci, almost the exclusive cause of late-onset disease, are the predominant group B isolates from pregnant and nonpregnant women as well as from nursery personnel (8, 58). Yow has summarized a Houston study showing marked increase in the rate of group B streptococcal colonization of neonates from birth to time of hospital discharge, 22.5 and 65.4%, respectively (154).

Although the precise pathogenesis of late-onset disease remains unclear, transient bacteremia with dissemination to other sites, especially the meninges, seems essential. Late-onset disease perhaps can also be the result of early asymptomatic infection due to acquisition of organisms in utero or at delivery, with subsequent invasion of other sites. Such spread to secondary target tissue can follow minor alterations to the normal flora that occur during an upper respiratory infection (9).

Histologically, late-onset disease shows the presence of a diffuse purulent leptomeningitis in affected infants (58).

LABORATORY DIAGNOSIS

Selective Broth Medium for Primary Isolation

Isolation of group B streptococci from blood, cerebrospinal fluid, urine, and other normally sterile sites in the body presents little difficulty. However, the divergence in human carrier rates reported for group B streptococci reflects a problem in significant growth or recognition of the organism from sites of mixed flora. In late 1973, Baker and colleagues (10, 11) described a selective broth medium designed to enhance group B isolation. This medium contained Todd-Hewitt broth with sheep blood, and incorporated nalidixic acid (15 μg/ml) and gentamicin sulfate (8 μg/ml). Use of the medium has resulted in more valid data from subsequent epidemiological investigations (Table 4, Baker and Barrett, Hafeez and Patterson).

TABLE 9. *Distribution of serotypes among parturient women, nursery personnel, and infants*

Serotype	Population							
	Mothers		Nursery personnel		Neonates with disease			
					Early onset		Late onset	
	A[a]	B[b]	A	B	A	B	A	B
Ia	8.5[c]	35.6	12.8	0	8	[65][d]	0	0
Ib	11	8.9	5.1	8.3	8		0	0
Ic	8.5	4.4	2.5	0	8		6	0
II	35	15.5	48.7	25.0	20	[35][e]	0	0
III	37	28.9	30.9	66.7	56		94	100

[a] From Baker and Barrett (7, 8).
[b] From Franciosi et al. (58).
[c] Percentage.
[d] BI subtypes, not differentiated.
[e] BII or BIII.

This medium is appropriate for screening women during pregnancy and at the onset of labor, as well as neonates after delivery attended by maternal or fetal complications.

A second screening procedure for high-risk neonates is Gram staining of gastric aspirate (1, 37). This provides rapid recognition of potential candidates for early-onset group B streptococcal disease.

Presumptive Identification

Definitive identification from a single colony of a putative group B streptococcus can be accomplished only by extraction of the group carbohydrate and serological identification of the extracted antigen with specific antibody. Because of the inherent delay from initial culture to final seroidentification, both presumptive biochemical methods and rapid serological techniques have been developed to provide prompt information to the physician.

The colonial appearance of the group B streptococcus on sheep blood agar at 24 h is distinct from that of group A or D, the other common human streptococcal pathogens. The colony is usually gray, soft, and mucoid, often larger than 2 mm and surrounded by a small hazy zone of beta-hemolysis (24). Although the group B hemolysin appears unrelated to the oxygen-labile streptolysin O (28), determination of hemolysis is usually performed by microscopic examination of subsurface growth or incubation under reduced oxygen tension (48). Nonhemolytic isolates occur rarely; of 311 isolates submitted to the Center for Disease Control (CDC), Atlanta, Ga., only 6 failed to produce detectable hemolysin, even when subsurface growth was observed microscopically (129). Isolation of a nonhemolytic strain of group B streptococcus from a human neonate has been documented (152). Pigment production, potentiated by prolonged incubation at room temperature, anaerobic incubation, or the incorporation of starch into the culture medium, is an unstable property (28).

A unique combination of biochemical reactions allows presumptive identification of the putative group B colony, as shown in Table 10. This table is a compilation of data from a study of over 4,500 specimens submitted to the Streptococcus Laboratory, CDC. Susceptibility to bacitracin, often the first test run on a beta-hemolytic streptococcal isolate in the clinical microbiology laboratory, is subject to interpretive error (48). As can be seen, approximately 94% of group B streptococci are resistant to bacitracin. Nearly 80% of group B organisms grow in the presence of high salt. Historically, one of the earliest tests differentiating *S. agalactiae* from other streptococci was assessment of the ability of these organisms to hydrolyze sodium hippurate to benzoate and glycine (6). This test remains the most important part of the identification battery for group B organisms. Nearly all group B streptococci are positive for this character. Hippuricase activity is found also in the group D streptococci, but over 99% of the latter can hydrolyze esculin in the presence of bile, whereas no group B organisms exhibit this property. Isolation, partial purification, and characterization of the hippuricase factor by Ferrieri and colleagues (52) reveal a heat-labile, trypsin-sensitive enzyme with a pH optimum of 7.1 to 9. The enzyme is an intracellular component of live or killed whole cells, not released extracellularly during normal growth and not associated with cell membranes or cell walls. The hippuricase factor from group B type Ic streptococci is antigenic in rabbits and appears immunologically identical to that of types Ia, Ib, II, and III by microtiter neutralization of enzymatic activity (52).

An ancillary factor for the identification of group B streptococci, long utilized in veterinary microbiology, is the CAMP factor, named for the scientists originally describing the phenom-

TABLE 10. *Reactions useful in the presumptive identification of certain streptococci*[a]

Procedure	Identification			
	Group A	Group B	Not group A, B, D	Group D
Hemolysis	Beta	Beta	Beta	Beta, alpha, or none
Bacitracin susceptibility	+ (99.5)[b]	− (6.0)	− (7.5)	− (1.1)
Hydrolysis of esculin in presence of 40% bile	− (0)	− (0)	− (<0.3)	+ (99.5)
Tolerance to 6.5% NaCl	− (1.9)	±[c] (79.2)	± (15.4)	± (79.5)[d]
Hydrolysis of sodium hippurate	− (0)	+ (99.6)	− (0.3)	− (5.4)

[a] From Facklam et al. (48).
[b] Percentage of positive and negative strains among total strains examined.
[c] Variable reactions.
[d] The group D enterococci are 99.6% positive.

enon (33). The CAMP factor is thought to be a diffusable, heat-stable extracellular protein of group B organisms that enhances rapid hemolysis of sheep erythrocytes by staphylococcal beta-hemolysin (25, 47). Classically, the reaction is produced by streaking the staphylococcal strain across the diameter of a sheep blood agar plate, and the streptococcal strains to be assayed perpendicular to the staphylococcal streak. Positive reactions are indicated by an arrowhead pattern of hemolysis after overnight incubation at 37°C, and the reaction is enhanced by anaerobiosis (33). Even some of the nonhemolytic group B streptococci can potentiate this hemolytic phenomenon (129).

Serological Identification

Definitive identification of streptococci rests upon immunological reactivity with specific antisera prepared against the group and type antigenic moieties. The prototype precipitin test, discussed in the earlier section on seroclassification, is the classic diagnostic technique. Extraction of carbohydrate antigens for the precipitin assays is accomplished by one of several methods: the original acid extraction of Lancefield (85), the formamide method of Fuller (61), use of an enzyme from *Streptomyces albus* described by Maxted (103) and McCarty (104), use of the protease of *Streptomyces griseus* introduced by Ederer (38), or simply by autoclaving as shown by Rantz and Randall (122).

Romero and Wilkinson have described a rapid fluorescent-antibody test for use on smears of suspected colonies (129). These authors stress proper preparation of the conjugate as critical. Successful conjugate contains type antigen in addition to specific group antigen, but not the R protein antigens that cross-react with other streptococcal groups. Type and group antigens are combined, since type antigens may sterically hinder binding of antibody to group antigens on the cell surface.

Use of counterimmunoelectrophoresis (CIEP) also provides a more rapid alternative to the capillary precipitin assay for extracted carbohydrate antigen. Edwards and Larson have demonstrated that CIEP possesses greater sensitivity (40), and additionally its speed and simplicity have been recognized in numerous other microbial assay systems (39, 42, 63). Hill and colleagues (72) have described a CIEP method employing Todd-Hewitt broth inocula of group B streptococci without an extraction step. This group also reported CIEP results of examination of body fluids from patients infected with group B streptococci. Cross-reactivity occurred with the reagents employed for the type I subtypes, but the method successfully separated types I, II, and III.

Edwards and Larson (41) have described an application of the coagglutination test, which can be performed directly on colonies, for grouping the streptococci. This method employs protein A-containing *S. aureus* adsorbed with specific streptococcal antibody. Binding of the Fc portions of immunoglobulin G molecules to cell wall protein A sites has been characterized for other antigen-antibody systems (81).

IMMUNOLOGY

Host Antibody Response

Group B streptococcal antigenicity and the host immune response to this organism have been investigated only preliminarily. The system of protective antibodies associated with group B has been elucidated by Lancefield and colleagues in the mouse model (90, 94). Wilkinson and Jones have recently described a radioimmunoassay for detection of the primary reaction between type-specific antigen and antibody in the group B streptococcal response (150).

It is known that human neonates show increased susceptibility to many infectious agents, in part due to immature chemotactic and immune mechanisms (153). Passive protection, acquired from the mother, contributes to the neonatal system of defense and has been shown to be responsible for the rarity of infant infections with the group A streptococci. Quinn and Lowry (117) and Zimmerman and Hill (156) have demonstrated the ability of antibodies to the M proteins, the virulence factors in group A, to cross the placenta. The recent work of Baker and Kasper (12) suggests similar transplacental transfer of maternal antibody to group B streptococci type III, which correlates with neonatal protection even in the presence of maternal genital colonization. Seven of seven sera from mothers whose infants had invasive type III disease did not have detectable antibody (12).

Klesius and colleagues have studied immune responsiveness to all the group B types, in particular Ia and III, using blood cells and sera from both human maternal-cord pairs and primates undergoing experimental infection (83). The humoral and cell-mediated components of the defense system identified in this study include agglutinins, opsonins, and a leukocyte phagocytic activity.

Agglutinins specific for only types Ib and III were detectable in maternal sera collected at delivery. Corresponding cord sera were positive for group B Ib but not group B III agglutinins,

indicating that the latter are of an antibody class unable to cross the placenta. It must be noted that streptococci of group B Ib, although often found in the vaginal flora, are the least frequent streptococcal type isolated from neonates (Table 3). The possible protective role of passive group B Ib agglutinins has been considered (83).

A second serum factor, a thermolabile opsonin against group B Ia, was detected in the plasma of about 5 to 10% of maternal-neonatal pairs (74, 83, 102). Corresponding titers of paired mother and infant sera show that this factor crosses the placenta. Characterization of the factor implicates participation of two components: a specific group B Ia opsonizing antibody and a factor involved with a complement component present in both the classic and properdin pathways. Similar serum factors specific for the other group B types have not been detected, although these strains are nonspecifically opsonized without the addition of complement in 95% of human or primate sera studied (102).

In a recent study of phagocytosis of group B streptococcal types Ia, Ib, and Ic, by rabbit alveolar macrophages, Anthony has demonstrated the presence in the sera of immunized rabbits of heat-stable opsonins to type-specific or shared, carbohydrate or protein, antigens (4).

Leukocytic Response

Presence of the thermolabile opsonin just described is associated with enhanced phagocytosis in vitro by both homologous and heterologous polymorphonuclear neutrophils (PMNs) (83). The phagocytic index (total streptococci ingested/50 PMNs) appears unaffected by the presence or absence of type-specific agglutinins. Phagocytic activity to all serotypes other than B Ia of human maternal and cord cells as well as primate PMNs was demonstrated in 85 to 100% of the samples. Only 5.9% of mothers, 8.3% of neonates, and 25% of primates in the study showed PMN activity against group B Ia. Presence or absence of phagocytic activity, as with the opsonin against group B Ia, appears to be the same for both members of maternal-neonatal pairs. In addition, the calculated phagocytic indexes from these studies show that ingestion of group B Ia organisms is significantly less than that of other serotypes.

In examination of the immune responsiveness of the only survivor of group B Ia streptococcal disease in their series, Horn and colleagues showed the presence of type-specific opsonins and increased phagocytic ability in mother as well as the patient (74).

Anderson and co-workers (3) have studied other in vitro assessments of leukocyte metabolism and antimicrobial function in infected infants, i.e., the hexosemonophosphate shunt activity (HMPS) and the reduction of nitroblue tetrazolium (NBT). Where there is normal leukocyte function, infecting organisms are rapidly phagocytosed in vivo. Leukocyte samples taken during bacterial infection reflect this activation by spontaneous in vitro reduction of the dye NBT to formazan. Reduction is evidenced by the increased deposition of intracellular blue-black granules in activated leukocytes compared with cells from controls with nonbacterial infection or without illness (112). In premature and term infants with proven bacterial sepsis, including one with group B streptococcal sepsis, the spontaneous in vitro NBT reduction was low. However, when leukocytes from these same children were stimulated in vitro by glass contact, NBT reduction rose to the range for leukocytes from normal neonates matched for gestational age (3).

During periods of heightened metabolic activity, leukocyte phagocytosis is normally followed by activation of the HMPS. Absence of HMPS activation in leukocytes taken from the same septic neonates even after in vitro stimulation with latex particles provides suggestive evidence of a functional leukocyte defect. However, in following two neonates through successful courses of therapy for *Haemophilus influenzae* type b meningitis and streptococcal group B sepsis, respectively, spontaneous NBT reduction and HMPS activity within the normal range were shown to correlate with clinical improvement (3).

These preliminary studies on host responsiveness to the group B organisms suggest that neonatal disease may be associated with lack of passive immunity, immaturity of the newborn's own immune system, or a functional defect of the phagocytic and bactericidal ability of the infant's leukocytes. Further investigation into the nature of the capsular polysaccharide antigen and of the host response, both natural and induced, active and acquired, is necessary.

EPIDEMIOLOGY

Incidence

Human disease attributed to group B streptococci shows widespread geographical distribution. Finn and Holden at a general hospital in Saskatoon, observed an increase from 1 clinical isolate in 1964 to 80 isolates in 1968, without change in laboratory protocol (55). Yow's survey of approximately 8,000 live births per year in a Houston obstetrics ward, during the pe-

riod 1967 to 1974, showed no definitive group B streptococcal isolation from infants with meningitis prior to 1970. From 1970 to 1974, however, group B streptococci were isolated from 7 to 14 cases of infant meningitis each year (154). Howard and McCracken in Dallas (76) have documented 0.69 cases of *E. coli* neonatal infection and 1.35 cases of group B streptococcal neonatal infection per 1,000 deliveries during a study period 1969 to 1973. In a retrospective study during 1974 of 22 cases of neonatal septicemia, Ablow and colleagues at Yale-New Haven Hospital (1) found a higher incidence of group B streptococci (11/22) than coliforms (7/22).

After a study period (1961 to 1963) when the group B streptococcus was the most frequently isolated single agent, responsible for 25% of cases of neonatal sepsis at Boston City Hospital, Eickhoff and colleagues reported the absence of this organism from subsequent cases of neonatal sepsis for over 2 years (44). As yet, there is no explanation for such variation in prevalence.

Source

Normal flora constituents of the vaginal-cervical area are influenced by age, pH, and glycogen content. Surveys of the bacteria associated with the parturient human urethra and cervix by de Louvois and colleagues (35) and White and Koontz (145) show that numerous other organisms are isolated more frequently than are group B streptococci. Among these more prevalent organisms are lactobacilli, diphtheroids, staphylococci, group D streptococci, yeast, and *E. coli*. It is thought that group B streptococcal colonization may originate just inside the vaginal introitus, perhaps associated with the Bartholin's gland. The ecological conditions of the pregnant cervix, an acidic milieu created by the lactobacilli and a glycogen-rich mucosa, seem conducive to growth of group B streptococci (123). A comparative study with controls matched for parity, age, and socioeconomic background must be undertaken to interpret recovery of group B streptococci from pregnant and nonpregnant women.

Transmission

Early-onset group B streptococcal disease, characterized by sepsis and acute respiratory distress, is presumably acquired from the maternal genital tract (7, 8, 9, 58). Late-onset disease, marked by a purulent leptomeningitis, is thought, as shown in Table 9, to be nosocomial in origin. Carrier prevalence, illustrated in Table 4, is affected by a number of variables, including laboratory methodology, number of specimens collected per individual, and number of sites cultured. Although the reported carrier rate varies markedly, it is clear that the female genital tract is a primary reservoir.

Whether the genital tract is seeded from an original fecal reservoir is not known. However, in one of the studies by Franciosi and colleagues (58), both fecal and genital specimens were taken and all positive genital specimens were accompanied by corresponding presence of the organism in the feces. Our own unpublished data of multiple-site cultures, as shown in Table 11, confirm this association and indeed show an instance of isolation from the gastrointestinal tract alone. In our larger series of similar patients, where single sites were evaluated, the fecal colonization rate (27.3%) exceeded both the cervical-vaginal (25.9%) and the throat (10.8%) colonization rates. Zahradnicky reported a family study with the index case an infant who died of group B sepsis (155). Both mother (vagina and cervix) and father (urethra) carried the same strain that was cultured from the child at autopsy. Despite aggressive antimicrobial therapy, the organism showed prolonged persistence in the gastrointestinal tracts of the parents and was considered responsible for intermittent recolonization of the genitalia. In summary, all these data lend support to the importance of a fecal reservoir for group B streptococci and suggest that even where genital colonization is asymptomatic there is a likelihood of sexual transmission of the organisms.

Microbial Persistence

An understanding of the dynamics of appearance and disappearance of group B streptococci in colonized individuals requires a large prospective study. The organism is not limited to

TABLE 11. *Site of colonization with group B streptococci*[a]

Sites culture positive	No. of patients (%)
Throat, vagina, rectum	6 (10.9)
Throat and rectum	1 (1.8)
Throat and vagina	0 (0)
Vagina and rectum	8 (14.5)
Throat	0 (0)
Vagina	0 (0)
Rectum	1 (1.8)
Colonization rate	16 29.1

[a]Unpublished data from Hafeez and Patterson based on 55 women of childbearing age cultured from three sites, using selective antibiotic broth medium (10, 11).

the gential tract of pregnant women but is a transient inhabitant of several body sites of children and adults. Long-term carriage is also possible. Group B streptococci were found to persist in the genital tract of two women, shown to have harbored group B streptococci at delivery, when follow-up examinations were done at 2 and 4 months postpartum (19), Horn and colleagues (74) described continuing maternal vaginal and paternal urethral carriage 6 weeks postpartum. In Zahradnicky's study, persistence for over 2 years with only transient disappearance of the same strain in both mother and father was observed (155).

Race

Although a higher proportion of infected white than black neonates has been observed in some studies (9, 70, 118), sufficient data have not been accumulated to show a definitive link of race or socioeconomic class with carriage of group B streptococcus and risk to the fetus.

Sex

The male-to-female ratio of neonatal disease attributed to group B streptococci as reported in the literature has been summarized in Table 12. The ratio is nearly equal in data accumulated to date. In previous surveys of neonatal sepsis and meningitis of all etiologies, there is a marked preponderance of males, 2:1 (22, 153), which is lacking in these data.

Other Factors

The influence of neonatal or obstetrical history on incidence of group B neonatal disease has been discussed in the section Clinical Disease Spectrum. Because the organism is an opportunist, maternal and neonatal factors (i.e., prolonged rupture of membranes or prematurity) can increase the risk of streptococcal morbidity. Both the decreased use of hexachlorophene in infant bathing and the effect of contraceptives on altering the normal female genital flora have been implicated in increased group B infection (105, 153), but control studies are lacking in these areas.

TABLE 12. *Sexual distribution of neonates with group B streptococcal disease*

Male-to-female ratio	Selected reference
2:9	Barton et al. (16)
15:18	Baker et al. (9)
23:20	Franciosi et al. (58)
9:8	Quirante et al. (118)
60:56	Baker and Barrett (8)

PROPHYLAXIS AND TREATMENT

Spectrum of Antimicrobial Susceptibility

Antibiotic susceptibility patterns for group B streptococci have been reported for several decades. In 1957, Jones and colleagues at Boston City Hospital noted that among strains of streptococci from groups A, B, C, D, F, and G collected during 1954 and 1955, the 55 strains of group B were the least susceptible to penicillin, although still well within serum levels achieved at usual dosages of this drug (78). Decreased susceptibility to erythromycin was also noted among the group B organisms. In an examination of approximately 150 strains collected at the same institution in 1962 and 1963 by Eickhoff and associates (43) and reviewed by Finland (53), several characteristics of the antimicrobial spectrum were observed. As shown in Fig. 1, the penicillin curve is almost vertical, indicating essentially the same penicillin minimum inhibitory concentration for all strains tested. A similar pattern was found for all the other antibiotics tested except erythromycin and the tetracycline analogues. Several strains highly resistant to erythromycin were identified. A bimodal distribution of the bacterial population into strains susceptible or resistant to tetracycline was shown. Our own survey of 56 isolates, collected in Lansing, Michigan, in 1973 and 1974, when compared in Fig. 1 with the strains described above, showed a shift in penicillin minimum inhibitory concentration values toward decreasing susceptibility. The preponderance of tetracycline-resistant strains in our recent survey reflects a definite shift toward resistance seen around the country (personal communications). Among the strains isolated in 1963, the order of decreasing antibiotic activity was: penicillin, erythromycin, the synthetic penicillins and cephalosporins, the tetracycline analogues, chloramphenicol, and the aminoglycosides. In a similar study done in France in 1971, Fleurette et al. showed a few erythromycin-resistant strains, bimodal distribution to tetracycline, and a similar pattern of decreasing antibiotic activity (56). Group B strains appear highly susceptible to lincomycin and clindamycin (5, 79).

Carrier Prophylaxis

Although the group B streptococci exhibit somewhat less susceptibility to penicillin than any of the other streptococcal groups, penicillin remains the drug of choice in treating either neonatal or adult disease. Although it is now recognized that group B streptococci contribute significant morbidity and mortality in the

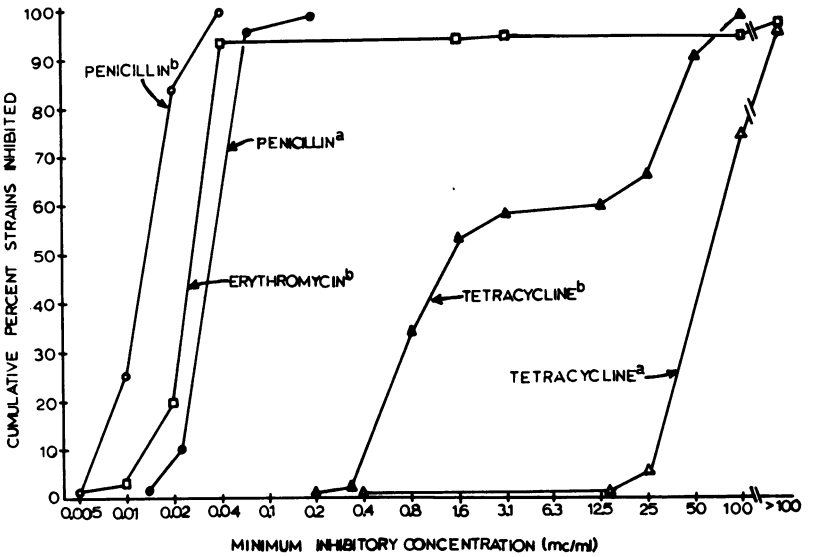

FIG. 1. *Susceptibility of group B streptococci to antibiotics. (a) From Hafeez and Patterson, unpublished data, 56 strains, collected in 1973 and 1974, East Lansing, Mich. (b) From Eickhoff and associates (43), 146 strains, collected 1962 and 1963, Boston, Mass. In both series, minimum inhibitory concentrations were determined by the agar dilution technique using the Steers replicating apparatus (138).*

neonatal period, recommendations for preventive chemotherapy are the subject of debate (29, 44, 49, 66).

Recommendations for prophylaxis include those of Franciosi and colleagues (58) or those of McCracken (104). The former suggest that vaginal cultures be done late in pregnancy and that eradication of the carrier state should be attempted with benzathine penicillin G for women positive by this screening procedure. The latter suggests that neonates be cultured at several sites for group B streptococcal colonization and treated if positive. The varied rates reported for maternal carriage (Table 4), reflecting number of sites and cultures taken over time, as well as different bacteriological techniques, should be considered before establishment of recommendations for prophylaxis.

The prophylactic approaches described have been the subject of both scientific and logistic criticism. There is evidence that sexual partners reinfect each other and that even in face of lengthy antibiotic treatment of both husband and wife, the carrier state is not necessarily eliminated (66, 155). In prophylaxis of colonized infants, similar long-term colonization despite the antibiotic regimen was reported (137).

The large numbers of pregnant women and their mates to be treated, in following the recommendations of Franciosi, would result in exposure of a sizable population to the risk of penicillin hypersensitivity and of undefined fetal reaction to the antibiotic. These risks should be recognized, analyzed, and balanced against the more defined risk of group B neonatal morbidity and mortality. Late-onset disease, nosocomial in origin, would probably be unaffected by prophylaxis of the approach suggested by Franciosi.

Recommendations for the chemotherapeutic treatment of colonized infants should be viewed in light of the disparity between risk of colonization and risk of disease (Table 8). Potentially 99% of colonized infants would be placed on penicillin prophylaxis unnecessarily. In addition, there are no data from any controlled study that show association between antibiotic therapy and decreasing incidence of group B disease.

In view of the probable sexual transmissibility of the agent, marked microbial persistence, risk to adults and possibly to fetuses of aggressive penicillin prophylaxis, and lack of data indicating comparative morbidity figures for prophylactically treated versus nontreated mothers or infants, a comprehensive study should be undertaken before major changes in medical practice are instituted.

Attention should be directed to immunoprophylaxis in a manner similar to that currently being investigated for *Haemophilus influenzae*, another pathogen of infants that possesses capsular polysaccharide antigens (12, 50, 108, 127, 144).

CONCLUDING REMARKS

Group B streptococci have been given a legitimate position among pathogenic members of the genus *Streptococcus*. These organisms have recently assumed a predominant role in a changed etiological spectrum of microorganisms associated with serious disease in human infants. The apparent shift in pathogenic significance of these agents has been ascribed to several factors, but essentially remains unclear.

The pathology and clinical disease manifestations associated with group B streptococci have been well documented. Certain epidemiological correlations have been established. Improvements in laboratory protocols for isolation and identification of these agents have permitted earlier, more accurate recognition. Antibiotic studies show that susceptibility of these organisms to penicillin has remained unchanged. However, many unanswered questions remain in all these areas. Investigation should be directed to the associations between carrier state and disease, site of carriage and culture success, eradication of maternal or neonatal carriage, and prevention of neonatal disease. Controlled studies with rigorous criteria are essential in an approach to these problems.

The precise balance between virulence of individual *S. agalactiae* serotypes and maternal or perinatal ability to resist infection should be clarified. Critical areas to be investigated include: nonspecific components of host resistance and the specific protective roles of the active and acquired immune mechanisms, cellular as well as humoral. All of these should be considered in relation to disease prevention. Continued investigation of already existing animal models should provide data necessary for greater insight into the problem of group B streptococcal disease.

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